

**REMARKS/ARGUMENTS**

**I. Status and Related Applications**

Claims 1-6 and 50-94 are under examination. In this response the specification and claims 1 and 50 are amended.

Applicants thank the Examiner for a detailed and helpful response in the Advisory Action mailed January 1, 2005. The comments below are in response to that Advisory Action.

Applicants wish to advise the Examiner of the following related patents and patent applications:

Application No.	(Filing Date)	Status
09/562195	(05/01/2000)	Granted (U.S. Pat. No. 6,783,934)
09/808674	(03/14/2001)	Granted (U.S. Pat. No. 6,713,297)
09/808706	(03/14/2001)	Pending
09/808877	(03/14/2001)	Abandoned
10/702538	(11/05/2003)	Pending

**II. Rejections Citing 35 USC 112, First Paragraph (Written Description)**

The claims were rejected under 35 USC 112, First Paragraph as allegedly failing to comply with the written description requirement.

As applicants understand this rejection, the Office asserts the specification does not adequately describe an apparatus for determining the threshold cycle number of application where "the device comprises but these two elements." As amended, claims 1 and 50 now recite the presence of a thermal cycler with which a nucleic acid amplification reaction can be conducted. The claimed apparatus would typically be used in combination with a reaction vessel or vessels in which the nucleic acid amplification reaction would take place. However, the vessel is not a component of the apparatus *per se*. For example, a reaction mixture can be prepared in a plastic reaction tube, and the tube placed in the thermal cycler of the claimed apparatus.

**III. Rejections Citing 35 USC 112, First Paragraph (Enablement)**

The claims were rejected as not enabled. The Office has asserted that claims are unpatentable if they "fairly encompass" elements not recited in the language of the claim.

However, every claim that uses the transitional phrase "comprising" encompasses elements not literally recited in the claim. The Office states, for example, that the claims prior to amendment "fairly encompass" a device with "an infinite number of elements" and that such a device is not enabled. According to the reasoning set forth in the Action, any claim that recites "comprising" would fairly encompass an infinite number of elements and no such claim would be enabled. This clearly is not the law. Applicants respectfully submit the claims as amended are patentable.

The Office states Applicants fail to provide convincing evidence as to how the claimed apparatus is to function when there is no amplification vessel integral to the apparatus. The Office does not explain why the vessel must be "integral." Any number of widely used devices use reaction vessels (e.g., test tubes) not integral to the device. This is for increased convenience, less potential for contamination, and to avoid the need to clean the vessels after each use.

The Office also states the specification is deficient because none of the examples teach formulas to be used in conducting first, second or subsequent derivatized growth curves . . . that can be used . . . for any and all manner of amplification reactions . . ." Applicants disagree with the Office's interpretation of the specification and law, but in the interest of expediting prosecution Applicants respectfully note that the amplification reactions for which the claimed device is used are thermal cycling amplification reactions. Applicants submit the specification provides ample guidance for one of skill to practice the invention.

#### IV. Rejection Under 35 USC §101

The Office states Applicants have not presented evidence as to how the claimed apparatus is to function when there is no amplification vessel integral to the claimed apparatus. Applicants have explained above that a reaction vessel can be placed in the apparatus (e.g., placed in the thermal cycler). The device no more lacks utility than does a refrigerator with nothing in it, a lamp without a bulb, or a syringe without a needle. In each case one of ordinary skill would understand that in using the refrigerator, lamp or syringe the device is combined with a companion element. Applicants submit the instantly claimed invention is useful.

V. Double Patenting

The Office stated claims 1-5 and 50-94 were rejected under the doctrine of obviousness-type double patenting over claims 1-48 of U.S. Patent No. 6,713,297 ("the '297 patent"). Applicants have previously traversed the rejection and explained that to establish a *prima facie* case of obviousness-type double patenting the Office must set forth the basis for alleged obviousness, including the reasons a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is an obvious variation of the invention defined in a claim of the patent. See MPEP 804(II)(b)(1).

In response the Office stated the claims of the instant application are "sufficiently broad so to encompass the use of quantitative internal controls." The Office stated claim 1 of the '297 patent, if read to incorporate the elements of dependent claims 21 and 22, require "that one calculate a threshold cycle number, a limitation of the claimed invention."

It appears that the Office asserts there are some similarities in the device of the '297 patent and that instantly claimed or that elements of each claim set might "encompass" elements of the other. Although the reasoning for the rejection is not entirely clear, *arguendo*, some similarities would not be wholly surprising, given that the '297 patent is an ancestor of the instant application this. Nonetheless, the test for obviousness-type double patenting is not similarity, or elements in common or "encompassed," but rather obviousness. See MPEP §804(II)(B)(1). The Office has not explained why one of ordinary skill in the art could consider the invention of the '297 patent an obvious variation of the instantly claimed device.

Further, although the reasoning underlying this rejection is not entirely understood by Applicants, to the extent the concern of the Office is the Office's belief that that '297 patent claim requires a calculation that is a limitation of the claimed invention Applicants note that such a situation would not be basis for a double patenting rejection. See MPEP §804(II):

Domination and double patenting should not be confused. They are two separate issues. One patent or application "dominates" a second patent or application when the first patent or application has a broad or generic claim which fully encompasses or reads on an invention defined in a narrower or more specific claim in another patent or application. Domination by itself, i.e., in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection. *In re Kaplan*, 789 F.2d 1574, 1577-

78, 229 USPQ 678, 681 (Fed. Cir. 1986); and *In re Sarrett*, 327 F.2d 1005, 1014-15, 140 USPQ 474, 482 (CCPA 1964).

Further, Applicants note the '297 claims are directed to an apparatus for determining an unknown starting quantity of a target nucleic acid sequence in a test sample and the instant claims are generally directed to an apparatus for determining a threshold cycle number in a nucleic acid amplification reaction, and the two applications are related as follows:

app. #	10/027,404	con of	09/808,674	divisional of	09/562,195
pat. #			6,713,297		6,783,934

In prosecution of the '195 patent restriction was required between claims drawn to a method of determining a threshold cycle number and claims to determining a quantity of nucleic acid in a sample (see Paper Number 4, mailed Dec 26, 2000). Further, *in the instant application*, restriction was required between claims drawn to a method of determining a threshold cycle number and claims to determining a quantity of nucleic acid in a sample (see Paper Number 0303, mailed March 25, 2003). ***This history of restriction should itself be dispositive of the issue of double patenting.***

To expedite prosecution and for convenience of the Office, Applicants have also prepared the table below, in which claim 1 of the '297 patent and claim 1 of the instant patent, plus elements of claims 21 and 22 of the instant patent (in italics) are reproduced. Applicants have aligned the claims according to linguistically similar phrases, but encourage the Examiner to do his own alignment if this table is found helpful. Should this rejection be maintained, Applicants respectfully request the Office make clear "(A) The differences between the inventions defined by the conflicting claims -- a claim in the patent compared to a claim in the application; and (B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim in issue is an obvious variation of the invention defined in a claim in the patent." MPEP §804(II)(B)(1).

'297	Instant Application
1. An apparatus for determining an unknown starting quantity of a target nucleic acid sequence in a test	1. An apparatus for determining a threshold cycle number in a nucleic acid amplification

sample, the apparatus comprising:	reaction, the apparatus comprising:
	a) a thermal cycler suitable for a nucleic acid amplification reaction;
<p>a) at least one detection mechanism for measuring:</p> <p>i) signals indicative of the respective quantities of the target nucleic acid sequence and of a first internal control being amplified in a first nucleic acid amplification reaction, wherein the first internal control comprises a second nucleic acid sequence different than the target nucleic acid sequence;</p> <p>ii) signals indicative of the respective quantities of a first standard and of a second internal control being amplified in a second nucleic acid amplification reaction, wherein the first standard comprises a first known starting quantity of a calibration nucleic acid sequence different than the second nucleic acid sequence, and wherein the second internal control comprises the second nucleic acid sequence;</p> <p>iii) signals indicative of the respective quantities of at least a second standard and of a third internal control being amplified in a third nucleic acid amplification reaction, wherein the second standard comprises a second known starting quantity of the calibration nucleic acid sequence, the third internal control comprises the second nucleic acid sequence, and the starting quantity of the second nucleic acid sequence is substantially equal in each of the amplification reactions;</p>	<p>b) at least one detection mechanism for measuring,</p> <p>at a plurality of different times during the amplification reaction, at least one signal whose intensity is related to the quantity of a nucleic acid sequence being amplified in the reaction; and</p>
<p>b) at least one controller in communication with the detection mechanism, wherein the controller is programmed to perform the steps of:</p> <p>i) determining from the measured signals respective threshold values for each of the standards, each of the internal controls, and the target nucleic acid sequence in the test sample</p> <p>ii) normalizing the threshold value determined for the target nucleic acid sequence in the test sample to the threshold value determined for the first internal control;</p> <p>iii) normalizing the threshold values determined for the first and second standards to the threshold values determined for the second and third internal controls, respectively;</p> <p>iv) deriving a calibration curve from the known starting quantities and the normalized threshold values of the standards; and</p> <p>v) determining the starting quantity of the target</p>	<p>b) a controller in communication with (i) a thermal cycler and (ii) the detection mechanism, wherein the controller is programmed to perform the steps of:</p> <p>i) deriving a growth curve from the measurements of the signal;</p> <p>ii) calculating a derivative of the growth curve;</p> <p>iii) identifying a characteristic of the derivative; and</p> <p>iv) determining the threshold cycle number associated with the characteristic of the derivative.</p>

nucleic acid sequence in the test sample using the calibration curve and the normalized threshold value determined for the target nucleic acid sequence

by

1) storing signal values defining a growth curve for the standard, internal control, or target nucleic acid sequence, wherein the growth curve expresses signal intensity as a function of cycle number or as a function of time;  
2) determining a derivative of the growth curve, wherein the derivative is determined with respect to cycle number or time; and  
3) calculating a cycle number or time value associated with a characteristic of the derivative;  
wherein each of the threshold values comprises a cycle number.

VI. Request for Interview

Applicants believe an interview would expedite prosecution. The Examiner is requested to please contact the undersigned when the Examiner is ready to consider the case.

**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes there are any remaining issues, please call the undersigned applicant's representative at 650-326-2400 in order to expedite prosecution.

Respectfully submitted,



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